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Effect of ONO-1101, a novel short-acting β-blocker, on hemodynamic responses to isoflurane inhalation and tracheal intubation

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Abstract

Purpose. We investigated the effect of a new ultra-short-acting β-blocker, ONO-1101, on hemodynamic responses to isoflurane inhalation and tracheal intubation.

Methods. Fifty-four ASA PS 1 or 2 patients were randomly allocated to receive either ONO-1101, 0.04 mg·kg^{-1}·min^{-1}, or saline prior to tracheal intubation. Anesthesia was induced with thiamylal, 4 mg·kg^{-1}, and vecuronium, 0.15 mg·kg^{-1}. Tracheal intubation was carried out after 3 min controlled mask ventilation with 66% N_2O and 3% inspired isoflurane in oxygen. Heart rate and blood pressure were continuously recorded from the start of induction until 5 min after intubation. Plasma concentrations of catecholamines were measured before induction, 3 min after initiating inhalation of isoflurane, and 1 min after tracheal intubation.

Results. Significant increases in heart rate occurred in both groups in response to isoflurane inhalation and tracheal intubation, but the magnitude of the increase was significantly less in the ONO-1101 group. Blood pressure increased after tracheal intubation in the saline group but remained unchanged in the ONO-1101 group. Plasma concentrations of norepinephrine increased after induction and intubation in both groups, with no significant difference between the groups.

Conclusion. ONO-1101 infusion is effective for the attenuation of hemodynamic responses to isoflurane inhalation and tracheal intubation.

Key words: ONO-1101, β-Blocker, Isoflurane, Tracheal intubation, Hemodynamic responses

Introduction

Laryngoscopy and tracheal intubation often induce tachycardia, hypertension, and arrythmias resulting from the cardiovascular response to noxious stimulation during the induction of general anesthesia [1–3]. Many anesthesiologists use techniques and agents, such as deep anesthesia [4], opioids [5,6], β-blockers [7–10], and vasodilators [11–13], to attenuate these hemodynamic responses. The recently developed β-blocker ONO-1101 is characterized by an ultra-short action and high cardioselectivity [14]. This pharmacological potential may be appropriate to blunt the hemodynamic responses to laryngoscopy and intubation without adverse effects. Thus we investigated the effect of ONO-1101 infusion on the hemodynamic responses to isoflurane inhalation and tracheal intubation.

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Materials and methods

This investigation is a phase III clinical study of ONO-1101, and the protocol was approved by the institutional Human Research Ethics Committees. Written informed consent was obtained from 54 ASA PS 1 or 2 patients undergoing elective surgery. The patients were premedicated with atropine, 0.01 mg·kg^{-1}, and hydroxyzine, 1 mg·kg^{-1}, intramuscularly 30 min before the start of anesthesia. Intravenous cannulation was performed, and 5 ml·kg^{-1} of lactated Ringer's solution was infused prior to induction of anesthesia. The radial artery was also cannulated for measurement of blood pressure and blood sampling. The heart rate was measured by ECG monitoring. The patients were randomly allocated into two groups to receive ONO-1101 (group A, $n = 29$), or normal saline (group B, $n = 25$). In both groups, anesthesia was induced with thiamylal, 4 mg·kg^{-1}, and vecuronium, 0.15 mg·kg^{-1}. Controlled mask ventilation was initiated after diminution of the eyelash reflex with a gas mixture of 60% N_2O and 3% inspired isoflurane in O_2. At the same time, infusion of ONO-1101 was started in group A at a rate of 0.125 mg·kg^{-1}·min^{-1} for 1 min as a loading dose,

followed by a maintenance dose at $0.04\,mg \cdot kg^{-1} \cdot min^{-1}$. This dosage regimen was determined from the preliminary study, in which about 90% of the patients with tachycardia during anesthesia showed improvement with this regimen. In group B, saline was infused similarly. After 3 min of ventilation, laryngoscopy was performed for 15 s, and the trachea was intubated by a senior anesthesiologist. After intubation, ventilation was continued with a gas mixture of 60% N_2O and 1% inspired isoflurane in O_2 in both groups.

Heart rate (HR) and direct systolic, diastolic, and mean arterial blood pressure (SBP, DBP, and MBP, respectively) were continuously recorded starting before the induction of anesthesia and lasting until 5 min after intubation. The data were obtained at 1-min intervals after starting the infusion. The mean end-tidal carbon dioxide ($EtCO_2$) and isoflurane concentrations were monitored by a capnograph. Blood samples from the radial artery were drawn for measurement of plasma concentrations of epinephrine (E) and norepinephrine (NE) before the induction of anesthesia, 3 min after ventilation by mask, and 1 min after laryngoscopy. The blood samples were collected in ice-cold plastic tubes containing EDTA and centrifuged at 4°C. Plasma was stored at −20°C until analyzed. E and NE in plasma were determined by high-performance liquid chromatography [15]. The limit of sensitivity was $5\,pg \cdot ml^{-1}$ for each catecholamine. In group A, to measure plasma concentrations of ONO-1101, blood samples were taken 3 min after ventilation by mask, 1 min after laryngoscopy, and 15 min after the end of infusion of ONO-1101. The blood samples for measurement of ONO-1101 were collected in ice-cold tubes containing 100% ethanol and fully shaken to abolish serum esterase. The samples were stored at −20°C until analysed. ONO-1101 concentrations in plasma were determined by high-performance liquid chromatography [16]. The limit of sensitivity was $50\,ng \cdot ml^{-1}$.

All data are presented as means ± SD. Within-group comparisons were performed by repeated-measures ANOVA followed by the Wilcoxon signed-rank test. Differences between the groups were analyzed by one-way ANOVA and the Mann-Whitney U-test. A P value less than 0.05 was considered significant.

Results

Demographic data are presented in Table 1. There were no differences between the groups with respect to sex, age, height, or weight. One patient in group A whose laryngoscopy time was prolonged because of difficult intubation and one patient in group B who moved during tracheal intubation were excluded from this study. After 3 min of ventilation, the end-tidal concentrations of isoflurane were 1.8 ± 0.5% in group A and 1.9 ± 0.4% in group B, and there was no significant difference between the groups.

Table 2 shows SBP and HR changes during induction of anesthesia and after laryngoscopy and tracheal intubation. The baseline values of SBP and HR were similar between the groups. In group B, HR increased significantly after inhalation of isoflurane without a change of SBP, and both SBP and HR increased significantly 1 min after tracheal intubation compared with baseline values. In group A, HR increased significantly after inhalation of isoflurane but was lower than in group B, whereas SBP decreased significantly compared with baseline values. After laryngoscopy and tracheal intubation, HR increased significantly compared with baseline values, but the increase in HR was less than that in group B. SBP after tracheal intubation increased significantly compared with that before intubation but was not significantly different from the baseline value. Five minutes after tracheal intubation, HR recovered to the baseline value in group A but remained at a higher level in group B, whereas SBP decreased significantly in both groups, with a greater decrease in group A than in group B.

Table 1. Demographic data

Variable	ONO-1101 (group A)	Control (group B)
No. of patients	28	24
Male/female ratio	13/15	12/12
Age (yr)	47 ± 13	41 ± 10
Height (cm)	159 ± 8	159 ± 9
Weight (kg)	57 ± 9	56 ± 12

Plus-minus values are expressed as mean ± SD.

Table 2. Hemodynamic data

Group	ONO-1101 (group A)	Control (group B)
Heart rate (bpm)		
Baseline	80 ± 18	77 ± 16
Preintubation	100 ± 20[ac]	111 ± 18[a]
1 min after intubation	108 ± 16[ab]	126 ± 17[a]
5 min after intubation	77 ± 13[b]	95 ± 15[a]
Systolic blood pressure (mmHg)		
Baseline	146 ± 22	140 ± 15
Preintubation	127 ± 28[a]	137 ± 24
1 min after intubation	143 ± 26	156 ± 23[a]
5 min after intubation	107 ± 17[ab]	119 ± 17[a]

Values are expressed as mean ± SD.
[a] $P < 0.01$ *vs* baseline values.
[b] $P < 0.01$ *vs* control group.
[c] $P < 0.05$ *vs* control group.

Table 3. Catecholamine data

Group	ONO-1101 (group A)	Control (group B)
Norepinephrine ($pg \cdot ml^{-1}$)		
Baseline	181 ± 134	255 ± 103
Preintubation	409 ± 356[a]	444 ± 160[a]
1 min after intubation	708 ± 475[ab]	629 ± 224[ab]
Epinephrine ($pg \cdot ml^{-1}$)		
Baseline	88 ± 101	78 ± 82
Preintubation	30 ± 27[a]	37 ± 25
1 min after intubation	42 ± 26[a]	30 ± 16

Values are expressed as mean ± SD.
[a] $P < 0.01$ *vs* baseline values.
[b] $P < 0.01$ *vs* preintubation values.

Table 4. Plasma concentrations of ONO-1101 ($ng \cdot ml^{-1}$)

Preintubation	1 min after intubation	15 min after end of infusion
937 ± 393	1102 ± 615	105 ± 131

Values are expressed as mean ± SD.

Table 3 shows the changes in plasma NE concentration. The baseline values were comparable between the groups. In group B, NE concentration increased significantly after inhalation of isoflurane, and the increase was enhanced by laryngoscopy and tracheal intubation. The changes in group A were similar to those in group B, and there was no significant difference between the groups. Plasma E concentration decreased slightly after induction in group A, but there was no significant difference between the groups.

Table 4 shows the changes in plasma concentration of ONO-1101. The infusion dose produced concentration of 937 ± 393 $ng \cdot ml^{-1}$ prior to intubation and maintained a similar level 1 min after intubation. Fifteen minutes after the end of infusion, the plasma concentration decreased to about 10% of that during infusion.

Discussion

The results show that the administration of ONO-1101, a novel β-blocker, is effective for attenuation of the hemodynamic responses to laryngoscopy and tracheal intubation during induction with isoflurane. HR and SBP 1 min after intubation in the group receiving ONO-1101 were suppressed to 86% and 92% of those in the control group, respectively. Moreover, the administration of ONO-1101 attenuated the increase in HR associated with inhalation of isoflurane.

Attenuation of the hemodynamic responses to laryngoscopy and tracheal intubation is very important for the anesthetic management of any case. Roy et al. [17] suggested that the ischemic episodes seemed to be related most often to increases in HR and BP following intubation. Coleman et al. [18] demonstrated that this stress period was also associated with the appearance of cardiac arrhythmias in healthy patients. Thus, many anesthesiologists use several techniques or agents to attenuate hemodynamic responses during this period, including deep anesthesia, opioids, β-blockers, and vasodilators. In previous reports, several β-blockers, such as propranolol [7], labetalol [8], and metoprolol [18], were used to attenuate hemodynamic responses to laryngoscopy and intubation. However, these drugs have the disadvantages of long-lasting effect, poor cardioselectivity, and adverse effects, such as severe hypotension, bradycardia, acute cardiac failure, and bronchospasm. Therefore, there has been a need to develop a β-blocker with a short period of action and high cardioselectivity. Esmolol, which is available for clinical use in the United States, is an ultra-short-acting (50% recovery from blockade occurred in 9 min) and fairly cardioselective (β_1/β_2 = 33) agent [14]. It has been reported [5,9,10] that esmolol is effective at attenuating hemodynamic responses to laryngoscopy and intubation.

ONO-1101 is ultra-short-acting (50% recovery in 9 min) and eight times more cardioselective (β_1/β_2 = 255) than esmolol. In the preliminary study, HR significantly decreased about 10% during infusion of ONO-1101 at a dose of 0.04 $mg \cdot kg^{-1} \cdot min^{-1}$ in healthy volunteers, while BP was unchanged. HR recovered to baseline within 30 min after the end of infusion. In the present study, the increase in HR after tracheal intubation was attenuated to 86% of control. Myocardial ischemic signs and cardiac arrhythmias during induction of anesthesia and intubation did not appear in either group.

In this study, isoflurane was used as the inhaled anesthetic. Previous reports indicated that a rapid increase in the inspired concentration of isoflurane caused sympathoadrenal activation and increases in HR and BP [19,20]. The mechanisms involved in this sympathoadrenal response would be related to stimulation of airway sensory afferents, the baroreceptor reflex, and/or direct stimulation of the central nervous system [21]. In the present study, inhalation of 3% isoflurane during induction caused a significant increase in HR without an increase in BP. This increase in HR was significantly but not completely diminished by infusion of ONO-1101. However, the increase in plasma NE concentration was not suppressed by ONO-1101. This discrepancy remained 1 min after tracheal intubation. The results suggest that ONO-1101 attenuates the hemodynamic response to isoflurane inhalation and tracheal intubation by direct action on the cardiovascular

system. The infusion dose in the present study produced a plasma concentration of 937 ± 393 ng·ml^{-1} of ONO-1101 prior to intubation. Although this level of ONO-1101 is known to be clinically effective in blocking peripheral β-adrenergic receptors, a greater dose would be necessary for a complete block.

To attenuate the hemodynamic responses to induction of anesthesia and intubation by the use of pharmacological agents, the timing of administration and the dose of the agents are important. Ebert et al. [9] reported that either a 100- or 200-mg single bolus of esmolol given 90 s prior to laryngoscopy was effective in attenuating hemodynamic responses. Vucevic et al. [10] reported that continuous infusion of esmolol at a dose of 0.1 mg·kg^{-1}·min^{-1} about 10 min before laryngoscopy was effective. Neither study reported any adverse effects. In the present study, we investigated the infusion method, because it is difficult to maintain a long-lasting therapeutic concentration by bolus injection, and a high-dose bolus might cause adverse effects. A therapeutic concentration was reached prior to laryngoscopy and was maintained thereafter. Moreover, there were no adverse effects during induction.

There are some limitations to the present research. First, we used ONO-1101 at only one dose, 0.04 mg·kg^{-1}·min^{-1}, and did not obtain a dose-effect relationship. Second, we recorded the hemodynamic parameters at 1-min intervals, so that the values obtained might not represent the maximum changes. However, previous reports indicated that the maximum changes in HR and SBP would occur between 30 and 60 s after intubation. Thus we regarded the values 1 min after intubation as the maximum values.

In conclusion, ONO-1101, a novel ultra-short-acting β-blocker, is effective for the attenuation of hemodynamic changes resulting from isoflurane inhalation and tracheal intubation.

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